3. LITERATURE REVIEW

Diabetes mellitus, a metabolic disorder, is becoming a serious threat to health of people. The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030\(^1\). The people with diabetes in the world are expected to approximately double between 2000 and 2025. India leads the world with largest number of diabetic subjects being termed as ‘diabetes capital of the world’ \(^2\), \(^3\). Plants have been used since time immemorial for medicinal purposes and form the origin of much of modern Pharmacotherapy. Many plants are reported to be useful in the treatment of Diabetes mellitus.

“Neerizhivu choornam”\(^29\) is a polyherbal Siddha formulation useful in the treatment of Diabetes. Literature survey on Neerizhivu choornam was carried out from various books, journals reputed libraries and also from various websites, online publishers on ethnobotony, Pharmacognosy, phytochemistry and pharmacological aspects. The literature review revealed that the “Neerizhivu choornam” is scientifically under explored. Further the ingredients of “Neerizhivu choornam” have been proved to be Hypoglycemic, Anti-hyperglycemic, Anti-diabetic and Hypocholestrolemic. Phyto-formulation studies of “Neerizhivu choornam” has not been carried out till date.

Neerizhivu chooranam consists of fine powders of Pericarp of Terminalia chebula (Tam: Kadukkai), Whole plant of Murraya konigii (Tam: Karuveppilei), Pericarp of Embilica officianalis (Tam: Nellivatral), Seeds of Syzygium cumini (Tam: Naval Kottai), Stem of Tinospora cardifolia (Tam: Seenthil), Whole plant of Phyllanthus amarus (Tam: Kizanelli) and Rhizome of Cyperus rotundus (Tam: Koraikizhangu). Polyherbal formulation in powdered form where the botanical ingredients are not more than ten can be evaluated microscopically. The hypoglycemic activity of alcoholic extract of individual ingredients of Cyperus scariosus(Rhizome), Terminalia chebula (Pericarp), Tinospora cardifolia (Stem), Phyllanthus amarus (Whole Plant), Syzygium cumini (Seed), Embilica officianalis (Pericarp) and Murraya konigii (Whole Plant) has already been reported. In the present investigation Macro-microscopic, preliminary phyto-chemical, physico-chemical constants, Phyto-formulation studies and Pharmacological screening of the selected formulation will be carried out.
The literature related to the usefulness of the ingredients of Neerazhive Chooranam, in managing diabetics mellitus is briefly presented as follows;

*Terminalia chebula* (Combretaceae)

Prakash Chandra Gupta30., revealed the biological and pharmacological properties of *Terminalia chebula* Retz. (Haritaki). *Terminalia chebula* possesses antibacterial, antifungal, antiviral, antidiabetic, antimutagenic, anti-oxidant, antiulcer and wound healing properties. It also prevents cardiac damage and it is used for the treatment of kidney diseases. It is a mild safe and effective laxative in traditional medicine. *Terminalia chebula* and its phytoconstituents have therapeutic effects with no toxicity.

Rejesh Kannan V et al31., studied the antidiabetic activity on ethanolic extracts of fruits of *Terminalia chebula* Retz. (EETC) Alloxan induced diabetic rats. EETC showed the nil toxicity upto 500mg/kg BW. The effect of EETC 200mg/kg BW was compared with Glibenclamide (600mg/kg BW). The histopathological changes caused after induction of alloxan showed the granular cytoplasm, dilation, shrunken nuclei and inflammation which were reduced after treatment of the EETC 200mg/kg BW. The present study on EETC has been confirmed that having the pharmacological action against the diabetic condition.

Ranjeet Sawant et al32., evaluated phytoconstituents, bioefficacy and phytopharmacological activities of *Terminalia chebula*. This research shows various experimental studies conducted on bioactive compounds isolated from *Terminalia chebula* has prospective use in alleviating aging, cancer, various GIT disorders.
**Phyllanthus amarus** (Euphorbiaceae)

Sonia verma et al., reviewed traditional uses, phytoconstituents and pharmacological properties of *Phyllanthus amarus*.

Herbert O.C Mvagwu et al., evaluated the hypoglycaemic effects of aqueous extract of *Phyllanthus amarus* in alloxan induced diabetic albino rats. The extract at a dose 260mg/kg produced a significant (p<0.05) reduction in blood glucose level by 112% at 24hrs of oral administration. On the administration of 390mg/kg dose of extract, significant (p<0.001) reduction in blood glucose level of 41% on day 7 and 16% on day 14 were observed. The above the results indicates the presence of hypoglycaemic constituents in the plant, *Phyllanthus amarus* Schum.

Shetti A.A et al., screened antidiabetic effects of ethanolic leaf extracts of *Phyllanthus amarus* in alloxan induced diabetic mice. Oral administration of ethanolic leaf extracts (400mg/kg BW) for 45 days resulted in a significant (p<0.05) decline in blood glucose from 310.20 to 141mg/dl and significant recovery in body weight of diabetic mice. There was also a significant (p<0.05) reduction in the activity of glucose 6-phosphatase and fructose 1-6-diphosphatase in liver, further there was significant (p<0.05).Increase in the glucokinase in liver of diabetic mice when compared with that of diabetic control.

**Tinospora cordifolia** (Menispermaceae)

Chnadra sekhar Singh et al., evaluated antidiabetic activity of ethanolic extract of *Tinospora cordifolia* leaves. The probable mechanism by which *Tinospora cordifolia* may
act as an anti-hyperglycaemic drug is not through insulin secretion like sulfonyl ureas. It may be through some peripheral mechanism such as increasing the glycogen storage in liver or decreasing the glucose release from the liver. This study clearly shows that *Tinospora cordifolia* has significant anti-diabetic activity in diabetic animals and has an efficacy of 50-70% compared to insulin.

**Jitendra Mittal et al**\(^3^7\), reviewed *Tinospora cordifolia* is a multipurpose medicinal plant. This review describes the prominence of *Tinospora cordifolia* in therapeutics such as use of crude extract of plants for the amelioration of various diseases, morphology, growth constrains, biochemical composition, biological activity in the field of plant tissue culture, natural products and nano-biotechnology.

**Rajalakshmi M et al**\(^3^8\), revealed the anti-diabetic properties of *Tinospora cordifolia* stem extracts on Streptozotocin induced diabetic rats. The oral administration of various extracts (Hexane, Ethyl acetate and Methanol) of *Tinospora cordifolia* were found to have potent anti-diabetic activity that reduces blood sugar level in Streptozotocin induced diabetic rats.

**Nagaraja P et al**\(^3^9\), studied the antidiabetic activity of *Tinospora cordifolia* (Willd.) in Streptozotocin diabetic rats. The probable mechanism by which *Tinospora cordifolia* may act as an anti-hypoglycemic drugs is not through insulin secretion like sulfonyl ureas. It may be through some peripheral mechanisms, such as increasing the glycogen storage in the liver or decreasing the glucose release from the liver.
Patel D.K et al\textsuperscript{10}, reviewed natural medicine from plant source used for therapy of diabetes mellitus. This review has been presented in a very interactive manner showing geographical region for availability, part of plant used, mechanism of action and phytoconstituents responsible for particular action, it will be of great importance who interested readers to easily identified and go for further research.

\textit{Eugenia jambolana (Myrtaceae)}

Mamun ANM-or-Rashid et al\textsuperscript{41}, presented a review on medicinal plants with anti-diabetic activity. The effects of this plant may delay the development diabetic complication and correct the metabolic abnormalities. This review work stimulate the researchers for further research on the potential use of medicinal plants having anti-diabetic potential.

Arun Vannan M et al\textsuperscript{42}, published an overview on anti-diabetic activity of Siddha medicinal plans. In their review, ethanolic extract of whole fruit of \textit{Eugenia jambolana} lowered blood glucose concentration probably by stimulating insulin secretogogue activity and increased the glycogen stored in muscle of normal rats.

Shweta Sharma et al\textsuperscript{43}, reviewed pharmacological activity of \textit{Syzygium cumini} extracts using different solvents and their effective doses. In this review, it was concluded that this plant is highly beneficial for the treatment of diseases and for the prevention of disease like diabetes, inflammation, hyperglycaemia and CNS related diseases.

Mohammed Al-Amin Sikder et al\textsuperscript{44}, studied active hypoglycemic fraction from \textit{Syzygium cumini} L. seed and its safety profile. The petroleum ether soluble fraction of the
methanol extract exhibited a rapid and significant (p<0.001) hypoglycemic action after a week of regular treatment (100 nad 300 mg/kg.BW). The safety profile was confirmed through liver function tests. Besides, the histopathological study of the liver, heart, kidney and spleen tissues of the experimental rats demonstrated no untoward effects of this petroleum ether soluble fraction to the treated diabetic rats.

Modi D.C et al\textsuperscript{45}, revealed the Pharmacognostic study of the seed of Syzygium cumini Linn. The present investigation, the detailed pharmacognostic study of Syzygium cumini leaf is carried out to lay down the standards which could be useful in future experimental studies.

Md.Rashedul Alam et al\textsuperscript{46}, evaluated the anti-diabetic, Phytochemical in Syzygium cumini (L). Skeels. (Myrtaceae). From the NMR data 4 different compounds Lupeol, 12 oleanen-3-ol-3β acetate, Stigmasterol, β-sitosterol were identified from n-hexane fraction of plant extract. These compounds have potential anti-diabetic activities which support the traditional use of the leaves as being remedy for treating diabetes.

Kumar A et al\textsuperscript{47}, screened anti-diabetic activity of Syzygium cumini and its isolated compounds against streptozotocin induced diabetic rats. A compound mycaminose was isolated from Syzygium cumini extract. The isolated compound 15mg/kg and ethyl acetate and methanol extracted compounds of Syzygium cumini seed 200 and 400mg/kg was undertaken to evaluate the antidiabetic activity against streptozotocin induced diabetic rats.
Cyperus rotundus (Cyperaceae)

Singh N et al\textsuperscript{48}, provided an overview on *Cyperus rotundus*. This study explore one of the cheapest and effective medicinal resources from this automatically growing plant all over India for the using thousands of arthritic conditions patients where more than 2% world population suffers from one kind or the other kinds of arthritis.

Sri Rangani Sivapalan \textsuperscript{49}, reviewed medicinal uses and pharmacological activities of *Cyperus rotundus* Linn.

Surendira kumar Sharma and Ajay Pal Singh\textsuperscript{50}, studied the morphological, microscopical and physiochemical investigation on the rhizomes of *Cyperus rotundus* Linn. The study includes Pharmacognostical evaluation by macroscopy, microscopy, powder analysis, fluorescence characteristic, WHO recommended physiochemical and Phytochemical procedures.

Emblica officinalis (Euphorbiaceae)

Algar Raja M et al\textsuperscript{51}, evaluated the standardization parameters and invitro anti-diabetic activity of *Emblica officinalis* fruits as per WHO guidelines. The TLC fingerprinting and fluorescence analysis of powdered fruits has been conducted and reported. The anti-diabetic activity is conducted by enzyme inhibition (α-glycosidase) in invitro methods on ethanolic extracts showed significant inhibition.
Saket Bihari Sharan et al52, studies in-vivo anti-diabetic activity of the methanolic and aqueous bark extract of the plant *Emblica officinalis* Gaertn. Results depicted that the maximum falloff blood glucose level of normal rats observed after 6 hrs during fasting blood glucose studies, with the dose of 250mg/kg identified as the most effective dose. The effect of bark extracts on serum lipid profile (cholesterol, triglycerides, HDL and LDL) were measured in diabetic rats. These evidence clearly indicates that the aqueous and methanolic extracs of *Emblica officinalis* stem barks have significant hypo-glycemic potential as well as anti-diabetic activity.

Tirgar P.R et al53, investigated the mechanism of action of anti-diabetic activity of *Emblica officinalis* on streptozotocin induced typr-1 diabetic rats. Treatment with fresh juice and the hydro-alcoholic extract produced significant increase in serum insulin level and AUC of diabetic rats compared to that of diabetic control.

*Murraya koenigii* (Rutaceae)

Sanjukta chatterji et al54, studied the glycemic effects of freeze dried *Murraya koenigii*. The finding of glycemic and Phytochemical studies suggest that the identified phytochemicals mightbe responsible for its glycemic effects and hence the freeze dried powder may be prescribed as adjunct to diatery therapy and drug treatment for managing diabetes mellitus.

Tembhurne SV and Sakarkar DM55, evaluated hypoglycemic effects of fruit juice of *Murraya koenigii* (L) in alloxan induced diabetic mice. The results of anti-diabetic
study reveals that the fruit juices of *Murraya koenigii* decreases blood glucose levels significantly at 10 and 15 day of administration (fasting serum glucose). It concludes that fresh juice of *Murraya koenigii* has hypoglycemic effects.

**Vinuthan MK et al**56. studied the effect of extracts of *Murraya koenigii* leaves on the levels of blood glucose and plasma insulin in alloxan induced diabetic rats. *Murraya koenigii* Spreng showed significant reduction (p<0.05) as compared to diabetic control groups. Plasma insulin showed significantly high on 43rd and 58th days of treatment in aqueous and methanolic extracts of *Murraya koenigii* treated group. This suggests that the hypo-glycemic effects may be mediated through stimulating insulin synthesis and/or secretion from the β-cells of pancreatic islets of langerhans.